Complete Summary

GUIDELINE TITLE

European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society.

BIBLIOGRAPHIC SOURCE(S)

Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinemic demyelinating neuropathies. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Soc. J Peripher Nerv Syst 2006 Mar;11(1):9-19. [60 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Paraproteinemic demyelinating neuropathy (PDN)

Note: Axonal neuropathies with a paraprotein are not part of the scope of these guidelines but are mentioned briefly.

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To construct clinically useful guidelines for the diagnosis, investigation, and treatment of patients with both a demyelinating neuropathy and a paraprotein (paraproteinemic demyelinating neuropathy [PDN]), based on the available evidence and, where evidence was not available, consensus

TARGET POPULATION

Patients presenting with paraproteinemic demyelinating neuropathy (PDN)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Investigation of a paraprotein including:
    - Serum immunofixation electrophoresis (SIFE)
    - Physical examination and assessment of signs and symptoms
    - Full blood count, renal and liver function, erythrocyte sedimentation rate, C-reactive protein, uric acid
    - Total immunoglobulin G (IgG), IgA, IgM concentrations
    - Radiologic x-ray skeletal survey (skull, pelvis, spine, ribs, long bones)
    - Ultrasound or computed tomography of abdomen and chest

Management/Treatment

1. IgM paraproteinemic demyelinating neuropathy (PDN)
    - Withholding immunosuppressive or immunomodulatory treatment and providing symptomatic treatment for tremor and paresthesiae in patients without significant disability
    - Intravenous immunoglobulin (IVIg)
    - Plasma exchange (PE)
    - Immunosuppressive treatment in patients with significant disability
2. IgG and IgA PDN

    - Therapeutic approach is similar to the approach in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
3. POEMS (signs of polyneuropathy, organomegaly, endocrinopathy, M band, and skin changes)
    - Consultation with hemato-oncologist
    - Local radiation or surgery
    - Melphalan with or without corticosteroids

MAJOR OUTCOMES CONSIDERED

- Sensitivity of diagnostic tests
- Effectiveness of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Task Force members searched MEDLINE from 1980 onwards on July 24, 2004, for articles on paraproteinemic demyelinating neuropathy (PDN) and "diagnosis" or "treatment" or "guideline" and used the personal databases of Task Force members. They also searched the Cochrane Library in September 2004.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This guideline has been produced by the Task Force members of the European Federation of Neurological Societies (EFNS) who are also members of the Peripheral Nerve Society (PNS). Additional non-European members of the Task Force were appointed on the recommendation of the Board of Directors of the PNS.

Methods for Reaching Consensus

Pairs of Task Force members prepared draft statements about classification, investigation, and treatment which were considered at a meeting in September 2004. Evidence was classified as classes I to IV, and recommendations were classified as levels A to C (see the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields). When only class IV evidence was available but consensus could be reached, the Task Force has offered advice as good practice points. The statements were collated into a single document that was revised iteratively until consensus was reached.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point (GPP) When only class IV evidence was available but consensus could be reached, the Task Force offered advice as good practice points.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (Hughes RAC, Barnes MP, Baron J, Brainin M [2001]. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces. *Eur J Neurol* 8:549-550).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point [GPP]) are defined at the end of the "Major Recommendations" field.

Investigation and Classification of the Paraproteins

The Table below suggests investigations to be considered in all patients with a paraprotein. Serum immunofixation electrophoresis (SIFE) should be performed in all cases of known paraprotein to define the heavy- and light-chain types, in all acquired demyelinating neuropathies, and if a paraprotein is suspected but not detected by standard serum protein electrophoresis (SPEP).

Table. Investigation of a Paraprotein

The following should be considered in all patients with a paraprotein:

1. Serum immunofixation electrophoresis
2. Physical examination for peripheral lymphadenopathy, hepatosplenomegaly, macroglossia, and signs of polyneuropathy, organomegaly, endocrinopathy, M band, and skin changes (POEMS syndrome) (see section "Other neuropathy syndromes associated with paraproteinemia" in the original guideline document)
3. Full blood count, renal and liver function, calcium, phosphate, erythrocyte sedimentation rate, C-reactive protein, uric acid, beta 2-microglobulin, lactate dehydrogenase, rheumatoid factor, serum cryoglobulins
4. Total immunoglobulin G (IgG), IgA, IgM concentrations
5. Random urine collection for the detection of Bence-Jones protein (free light chains), and, if positive, 24 h urine collection for protein quantification
6. Radiographic x-ray skeletal survey, including skull, pelvis, spine, ribs, long bones (shoulder to wrist, and hip to ankle), to look for lytic or sclerotic lesions. If this is negative, then a Technetium-99 (Tc-99)m sesta-MIBI (2-methoxy-isobutyl-isonitrile) scan if high degree of suspicion of myeloma (IgA lambda and IgG lambda paraproteins are more frequently associated with osteosclerotic myeloma)
7. Ultrasound or computed tomography of abdomen and chest (to detect lymphadenopathy, hepatosplenomegaly)

Table. Investigation of a Paraprotein
8. Consultation with a hematologist and bone marrow examination (morphology, immunophenotype, and biopsy)

Is the Paraprotein Causing the Neuropathy?

Table. Causal Relationship between Paraprotein and Demyelinating Neuropathy
1. Highly probable if immunoglobulin M (IgM) paraprotein (monoclonal gammopathy of uncertain significance [MGUS] or Waldenstrom's) and: a. High titers of anti-myelin-associated glycoprotein (anti-MAG) or anti-GQ1b antibodies, or b. Nerve biopsy shows IgM or complement deposits on myelin, or widely spaced myelin on electron microscopy
2. Probable if either: a. IgM paraprotein (MGUS or Waldenström's) with high titers of IgM antibodies to other neural antigens (GM1, GD1a, GD1b, GM2, sulfatide, etc.), and slowly progressive predominantly distal symmetrical sensory neuropathy, or b. IgG or IgA paraprotein and nerve biopsy evidence (as in1b but with IgG or IgA deposits)
3. Less likely when any of the following are present in a patient with MGUS and without anti-MAG antibodies (diagnosis may be described as 'chronic inflammatory demyelinating polyradiculoneuropathy with coincidental paraprotein'): a. Time to peak of neuropathy <6 months b. Relapsing/remitting or monophasic course c. Cranial nerves involved (except chronic ataxic neuropathy with ophthalmoplegia, IgM monoclonal gammopathy, cold agglutinins, and disialoganglioside [CANOMAD]) d. Asymmetry e. History of preceding infection f. Abnormal median with normal sural sensory action potential g. IgG or IgA paraprotein without biopsy features in 2b

Cerebrospinal Fluid and Nerve Biopsy

Cerebrospinal fluid (CSF) examination and nerve biopsy may be helpful in selected circumstances (see Table, below, **good practice points**) but are not usually necessary if there is clearly demyelinating physiology with monoclonal gammopathy of uncertain significance (MGUS).

Table. Cerebrospinal Fluid (CSF) Examination and Nerve Biopsy
1. CSF examination is most likely to be helpful in the following situations: a. In patients with borderline demyelinating or axonal electrophysiology

Table. Cerebrospinal Fluid (CSF) Examination and Nerve Biopsy
or atypical phenotype, where the presence of raised CSF protein would help suggest that the neuropathy is immune mediated b. The presence of malignant cells would confirm lymphoproliferative infiltration
2. Nerve biopsy (usually sural nerve) is most likely to be helpful when the following conditions are being considered: a. Amyloidosis b. Vasculitis (e.g., due to cryoglobulinemia) c. Malignant lymphoproliferative infiltration of nerves, or d. Immunoglobulin M paraproteinemic demyelinating neuropathy (IgM PDN) with negative anti-myelin-associated glycoprotein antibodies, or IgG or IgA PDN with a chronic progressive course, where the discovery of widely spaced myelin on electron microscopy or deposits of immunoglobulin and/or complement bound to myelin would support a causal relationship between paraprotein and neuropathy. However, clinical decisions on treatment are often made without a biopsy.

Treatment of Paraproteinemic Demyelinating Neuropathy (PDN)

Good Practice Points for Treatment of IgM PDN

1. In patients without significant disability, consideration should be given to withholding immunosuppressive or immunomodulatory treatment, providing symptomatic treatment for tremor and paresthesiae, and giving reassurance that symptoms are unlikely to worsen significantly for several years.
2. In patients with significant disability or rapid worsening, intravenous immunoglobulin (IVIg) or plasma exchange (PE) should be considered as initial treatment, although their efficacy is unproven.
3. In patients with moderate or severe disability, immunosuppressive treatment should be considered, although its long-term efficacy remains unproven. Preliminary reports suggest that rituximab may be a promising therapy.
4. More research is needed.

Good Practice Points for Treatment of IgG and IgA PDN

In patients with a chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)-like neuropathy, the detection of IgG or IgA MGUS does not justify a different therapeutic approach from CIDP without a paraprotein.

Good Practice Points for Treatment of POEMS (signs of polyneuropathy, organomegaly, endocrinopathy, M band, and skin changes)

1. Patients should be managed in consultation with a hemato-oncologist.
2. Local radiation or surgery should be considered as the initial treatment for isolated plasmacytoma.
3. Melphalan (with or without corticosteroids) should be considered for patients with multiple or no detectable bone lesions.

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

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Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

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Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point (GPP) When only class IV evidence was available but consensus could be reached, the Task Force offered advice as good practice points.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis, investigation, and treatment of paraproteinemic demyelinating neuropathy (PDN)

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases. This guideline is not intended to have implications regarding reimbursement.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

IMPLEMENTATION TOOLS

Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinemic demyelinating neuropathies. Report of a joint task force of the European

Federation of Neurological Societies and the Peripheral Nerve Soc. J Peripher Nerv Syst 2006 Mar;11(1):9-19. [60 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Mar

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society
Peripheral Nerve Society - Disease Specific Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The following authors have reported conflicts of interest as follows:

R. Hughes, personal none, departmental research grants or honoraria from Bayer, Biogen-Idec, Schering-LFB, and Kedrion

D. Cornblath, personal honoraria from Aventis Behring and Baxter

C. Koski, personal honoraria from American Red Cross, Baxter, Bayer, and ZLB-Behring

J. M. Leger, personal none, departmental research grants or honoraria from Biogen-Idec, Baxter, Laboratoire Francais du Biofractionnement (LFB), and Octapharma

E. Nobile-Orazio, personal honoraria from Kedrion, Grifols, Baxter, and LFB (and he has been commissioned by Kedrion and Baxter to give expert opinions to the Italian Ministry of Health on the use of IVIg in dysimmune neuropathies)

J. Pollard, personal none, departmental research grants from Biogen-Idec and Schering

P. van Doorn, personal none, departmental research grants or honoraria from Baxter and Bayer

The other authors have nothing to declare.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site.

Print copies: Available from Dr. Robert Hadden, Department of Neurology, King's College Hospital, Denmark Hill, London SE5 9RS, UK; E-mail: rob.hadden@doctors.org.uk

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site.
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the European Federation of Neurological Societies Web site.
- Continuing Medical Education questions available from the European Journal of Neurology Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 8, 2006. The information was verified by the guideline developer on January 2, 2007.

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